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When should FDG-PET be used in the modern management of lymphoma?

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When should PET be used in the modern management of lymphoma?

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Summary

Positron Emission Tomography (PET) is a functional imaging technique which combined with CT (PET-CT) is increasingly used in lymphoma. Most subtypes accumulate Fluorodeoxyglucose (FDG) and its increased sensitivity, especially for extranodal disease, compared to CT makes PET-CT an attractive staging tool. 'Interim' PET-CT can be used to assess early response and end-of-treatment PET-CT to assess remission. Clinical trials are currently seeking to establish whether the predictive value of PET-CT can be successfully used to guide individual treatment to reduce toxicity and/or to improve outcomes. Standardised methods for performing and reporting PET have been developed in the context of trials. The role of PET in transplantation selection is evolving as PET appears to be more accurate and prognostic than CT. The role of FDG PET-CT throughout the management course in patients with lymphoma is explored in this review and the potential role for FLT to image proliferation. (146 words)

Keywords: Positron Emission Tomography, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Clinical Trials, Imaging.

What is PET?

Positron Emission Tomography (PET) is a technique which images physiological processes in vivo by detecting radioactive emissions from Positron Emitting radioisotopes or 'tracers' injected into a patient. The most commonly used tracer is 18F-Fluorodeoxyglucose (FDG) which is a glucose analogue that reflects glucose metabolism. In cancer cells, there is increased uptake of FDG due to enhanced glucose transport, turnover and trapping. Other processes with increased glycolysis, such as infection and inflammation also have increased FDG uptake, but often to a lesser degree than malignancy.

Modern PET cameras are now combined with a CT scanner, enabling functional and anatomical information to be obtained during the same imaging session. CT and PET can be viewed separately, side-by-side or 'fused' with the PET scan overlaid on the CT in colour.

PET scans are usually reported using visual assessment. The intensity and locations of FDG avid disease are reported and distinguished from areas with high physiological uptake, such as the brain and the urinary system, where FDG is excreted. Scans are usually displayed according to the standardised uptake value (SUV) which is the activity of the tracer, corrected for patient weight and the administered radioactivity (Figure 1). The use of a fixed display, with images scaled to a common SUV level aids consistency of reporting, allowing uptake within the same patient to be assessed at during different time points during treatment and reducing the effect of patient weight on the level of tracer uptake. Using a fixed display, SUV measures may be used to compare regions of interest, most commonly the 'maximum' (SUVmax) is used to describe the intensity of uptake at disease sites.

The CT is used to localise the PET abnormalities and any additional findings on CT reported.

The CT may be acquired at full dose with intravenous and/or bowel contrast, as would commonly be performed during a stand-alone CT but the scan has to be acquired during normal breathing rather than full inspiration, to fuse with the PET which is acquired in steps over 15-25 minutes rather than during a single breath-hold. Alternatively the CT may be acquired at lower dose, which is more common practice. Then the CT is used a) to measure how Xrays are attenuated in the patient and apply a correction to the FDG images to give a truer appreciation of the tracer distribution and b) to accurately localise sites of FDG uptake.

Which Lymphomas can be imaged with PET ?

Most Lymphomas are FDG avid. In a series of 766 patients imaged with lymphoma, 100% of Hodgkin lymphoma (HL), 97% of Diffuse Large B cell Lymphoma (DLBCL) and 95% of Follicular Lymphomas (FL) were FDG avid (Weiler-Sagie et al., 2010). Less common aggressive subtypes were also reported to be universally FDG avid including Burkitt lymphoma, Mantle Cell lymphoma and aggressive T cell lymphomas. More variable avidity has been reported for small lymphocytic lymphoma (50-83%), extranodal marginal zone lymphoma (54-67%), and lymphomas that involve the skin (Elstrom et al., 2003; Tsukamoto et al., 2007; Weiler-Sagie et al., 2010).

Aggressive lymphomas tend to have higher uptake than indolent lymphomas. In a study of 97 patients with NHL, although there was some overlap amongst patients with indolent and aggressive disease in the low SUV range, all patients with indolent lymphoma had SUVmax <13 (Schoder et al., 2005). Using an SUVmax ≥ 10

distinguished aggressive from indolent disease with 81% specificity and 71% sensitivity. SUVmax also correlates with proliferation, measured by the Ki-67 index in lymph node and extranodal biopsies obtained from patients with indolent and aggressive lymphomas (Watanabe et al., 2010).

This suggests that FDG-PET may be used in patients with suspected transformation to direct biopsy.

What is the added value of PET for staging?

PET is more sensitive and specific for nodal and extranodal disease than CT (Schaefer et al., 2004) because abnormal FDG uptake may be observed in normal sized lymph nodes and uptake may be seen without changes in organ architecture, for example focal uptake may be present in a spleen with normal appearance and size on CT (Figure 2). Equally, slightly enlarged nodes may be reactive and will not accumulate FDG. Upstaging occurs more commonly than downstaging, although both occur and this influences management in a proportion of patients. Extranodal disease is more often identified with PET than CT within the bone and bone marrow (Figure 3), liver and spleen (Raanani et al., 2006) but also occasionally in the peritoneum. Small lung nodules may not be resolved by PET but these are usually visible on the accompanying CT. Cutaneous lesions tend to be less FDG avid than extracutaneous disease and it has been suggested that PET may have a role to detect extracutaneous disease in patients with Mycosis Fungoides, which confers a worse prognosis (Feeney et al., 2010; Otero et al., 2009). The brain is an area of high FDG avidity which in other diseases limits the ability to detect metastatic disease (Larcos & Maisey, 1996) but intracerebral lymphoma is highly FDG avid and PET has been used to distinguish toxoplasmosis from intracerebral lymphoma in HIV

patients (O'Doherty et al., 1997). Nonetheless, leptomeningeal disease which is diffuse and may be low volume is difficult to assess with PET and MR is the investigation of choice for initial assessment of CNS lymphoma.

The availability of a baseline scan improves the accuracy of subsequent response assessment (S. Barrington et al., 2011; Meignan et al., 2009; Quarles van Ufford et al., 2010). Baseline PET is also important for the accurate planning of radiotherapy treatment, especially with the use of newer techniques treating smaller volumes that traditional involved-field radiotherapy (IFRT). It is recommended that the use of 'involved-site' radiotherapy (Specht et al., 2013) and 'involved-node' radiotherapy (INRT) (Girinsky et al., 2007) should ideally be based on staging PET-CT rather than CT alone.

The frequency of management change resulting from using PET-CT for staging differs between patient series from approximately 10 - 50%, but on average is around 15% (M. Hutchings et al., 2006; Naumann et al., 2004; Partridge et al., 2000; Pelosi et al., 2008; Raanani et al., 2006; Wirth et al., 2008). Patients with apparently limited stage on CT with Follicular Lymphoma are a group where PET may have an important impact because up to 60% (Karam et al., 2006; Luminari et al., 2013; Wirth et al., 2008) of patients will have more advanced disease demonstrated using PET, which is not curable with radiotherapy and systemic treatment would be preferred.

The presence of uni or multi-focal disease in the bone marrow on PET-CT is more sensitive for the detection of bone marrow involvement than bone marrow biopsy in HL and aggressive NHL. Diffuse homogenous uptake may be seen with reactive hyperplasia in the marrow, especially in HL and does not necessarily indicate marrow involvement. In a study in 454 patients with HL, no patients with stage I or II

disease on PET-CT were upstaged by bone marrow biopsy. Of the whole group, 82 patients had marrow involvement by PET, 27 by biopsy. Of these 27 patients, 22 had extranodal disease anyway on PET, the remaining five patients were upstaged from stage 3 to 4 by biopsy but this did not change the treatment plan. Thus the biopsy did not alter management in a single patient (T. C. El-Galaly et al., 2012) suggesting that staging PET may be used in preference to biopsy to assess bone marrow involvement in HL. In this study, only the presence of focal uptake was considered to represent disease involvement.

In aggressive NHL, small volume disease, typically ≤ 10% marrow involvement or coexistent low grade lymphoma may be missed by PET but this is unlikely to affect prognosis or treatment (Campbell et al., 2006). In a recent study of 130 patients with DLBCL, 33 patients had marrow involvement on PET, 14 on biopsy (Khan et al., 2013). No case was classified as stage 4 based on biopsy alone. Patients with PET and biopsy evidence of marrow involvement had worse prognosis than the rest of the study population but these patients frequently had adverse factors predictive of high risk disease. 2 patients with marrow involvement on biopsy had normal marrow appearances on PET with <10% of the marrow involved. This also suggests a restricted role for bone marrow biopsy in DLBCL patients staged by PET-CT.

PET-CT is less sensitive than bone marrow biopsy for marrow involvement in indolent lymphomas, which is frequently diffuse, can be small volume and has low grade FDG uptake. The sensitivity was reported as only 46% in indolent lymphomas in a recent meta-analysis and BMB is indicated in preference to PET (Chen et al., 2011). BMB with detailed histological examination including immunohistochemistry and testing for clonality remains the gold standard in indolent lymphomas.

Is contrast enhanced CT necessary in addition to PET (CT) ?

PET-CT is now considered to be routine for staging patients with HL and aggressive NHL in many centres worldwide. What is less clear is whether a full dose contrast enhanced CT (ceCT) is required in addition to the low dose (ldCT) that is usually performed as part of the PET-CT examination. Several publications have compared the use of ceCT versus ldCT as part of the PET-CT scan for staging/restaging lymphoma patients. All found that PET-CT with ldCT demonstrated more lesions than ceCT alone (Elstrom et al., 2008; Raanani et al., 2006; Schaefer et al., 2004). The use of ceCT rather than ldCT as part of the PET-CT examination did not affect stage nor alter management in three series (Elstrom et al., 2008; Gollub et al., 2007; Pinilla et al., 2011) but in one series, the use of ceCT altered stage in 8/68 patients with NHL and 4/35 patients with HL, which affected management in 9 patients (Raanani et al., 2006). The detail on how management was affected was not reported, but in two further publications (Pinilla et al., 2011), the use of ceCT was felt to improve the detection of disease in the small bowel in two patients and additionally the pancreas (in one of these patients), but affected management in one patient only (Schaefer et al., 2004) . This suggests that ce-CT used in place of ldCT in the PET-CT examination does not often impact on lymphoma management.

Pragmatically, many patients will have a ceCT scan performed prior to PET-CT, in which case a ldCT will suffice for PET-CT. If PET-CT is performed first, then ceCT may be preferred in patients likely to undergo radiotherapy treatment, preferably in the anticipated treatment position. In patients on trials, where nodal or extranodal

size measurements are required, ceCT is also necessary and would be more convenient if performed as a single test at the same scanning visit where possible. For other patients, whether the additional radiation incurred with a ceCT is justified should be considered when choosing the optimal examination. Advantages reported for ceCT were due to the use of contrast material rather than the increased X-ray dose and there may be a role for regional low dose CT with contrast after PET-CT. If the ceCT is performed at staging and there is no additional benefit, subsequent examinations should be performed at lower dose.

What is the role of PET in early response assessment?

Metabolic changes precede changes in tumour size, which enables response to be assessed earlier in the course of treatment with PET than CT. Rapid reduction in FDG uptake during chemotherapy is associated with a good prognosis in patients with HL and persistent FDG uptake with a poor prognosis in advanced HL patients. The group at Guy's and St Thomas' first reported in 2005 on a retrospective analysis of 85 patients with HL that PFS and OS were significantly different according to whether the PET scan performed after 2 or 3 cycles of chemotherapy was reported as 'negative', had 'minimal residual uptake' (MRU) or was reported as 'positive'(Hutchings et al., 2005). Patients with a negative scan or MRU had 5y-PFS rates of 92% compared with 39% for patients with a positive scan. This was followed by five further reports after 2 cycles of chemotherapy in HL, involving 1066 patients treated with ABVD (Biggi et al., 2013; Cerci, Pracchia, et al., 2010; Andrea Gallamini et al., 2007; M.; Hutchings et al., 2006; P. L. Zinzani et al., 2012), three of which were prospective (Cerci, Pracchia, et al., 2010; Andrea Gallamini et al., 2007; M.; Hutchings et al., 2006). These studies also reported 2y or longer PFS rates of 90-96% for patients with early complete metabolic response (CMR) and PFS rates of

0%, 13%, 28%, 28%, 53% respectively for patients with positive scans, with poorer outcomes for patients with advanced disease (Andrea Gallamini et al., 2007; M.; Hutchings et al., 2006). PET was a better predictor of outcome than the IPS (Andrea Gallamini et al., 2007). A further study reporting outcomes in 96 patients with early stage non-bulky HL (Barnes et al., 2011) found no difference in PFS according to early or 'interim' PET although the PET carried out at the end of treatment was predictive of outcome, probably due to the very good prognosis of this patient group and the effect of RT use. Overall, RT was given to 56% of patients in this study and there was a higher tendency to giving radiotherapy to patients with positive iPET (88%) than patients with negative iPET (54%). A report in 69 patients treated with BEACOPP reported a 4y-PFS of 98 % for patients with a negative iPET versus 78% for patients with a positive iPET (p=0.016)(Markova et al., 2012). The ability of iPET to predict prognosis early in treatment is clearly influenced by the timing of the scan in relation to chemotherapy, the stage of disease and the treatment regimen. At present, iPET at 2-3 cycles has been shown to be predictive of outcome in advanced stage, ABVD-treated patients but extrapolation of these results to BEACOPP-treated patients is not advisable and the role of iPET in early stage patients receiving combined modality treatment is not yet clear.

These studies highlighted the potential to use PET to tailor treatment for the individual according to their response during chemotherapy. The good prognosis associated with a negative iPET has led to the question of whether short-course chemotherapy without radiotherapy is an option for patients with early- stage favourable HL who have a negative iPET scan during ABVD treatment rather than combined modality treatment.

The UK National Cancer Research Institute study group recently presented the first results of the RAPID trial involving 602 patients with HL who had a PET scan performed after 3 cycles of ABVD (Radford et al., 2012). The study included non-bulky stage I & IIA disease and was designed to exclude a difference of ≥7% between RT and no RT. Patients with a CMR on PET (defined as score 1 & 2 only using a 5-point scale) were randomised to receive IFRT or no further treatment, whilst patients with a positive scan (score 3-5) received one further cycle of ABVD and 30Gy IFRT. 3y-PFS in 420 randomised patients with PET negative scans was 93.8% in the group receiving RT and 90.7% in the group receiving no further treatment, (risk difference -2.9%, 95%CI -10.7 to 1.4%: the lower CI marginally exceeded the maximum allowable difference of -7% for non-inferiority). 3-year OS was 97.0% in the RT group versus 99.5% in patients with no further treatment. PFS and OS in the PET positive group was 85.9 % and 93.9% respectively with a median follow up of 46 months. These preliminary data suggest that patients with iPET score 1 or 2 after 3 cycles of ABVD have excellent prognosis with 3 ABVD alone but longer follow up will be required to assess the trade-off between disease control and risks of late treatment effects in this patient group. This is especially relevant in patients for whom the risks associated with RT may be lower, eg patients >35 years and when irradiation of female breast tissue and/or the heart is not required.

The H10 study from the EORTC is ongoing and was designed with randomisation to experimental or standard arms. The standard arm received 3 or 4 cycles of ABVD according to whether disease was classified as favourable (F) or unfavourable (U) followed by INRT 30Gy + 6Gy boost to sites of residual lesions. The experimental arm adopted a PET-based strategy and consisted of 2 cycles of ABVD followed by PET. If PET showed CMR, patients received 3 (F) or 4 (U) additional cycles of

ABVD and no RT. If PET was positive, patients received 2 cycles of escBEACOPP. The first planned interim analysis of 1137 patients was recently presented (Andre et al., 2012). In the favourable group, a total of 10 events occurred; 1 in the standard arm, 9 in the experimental arm (1y-PFS 100% and 94.9% for standard and experimental arms respectively, HR 9.36 (CI : 2.45 – 35.73). In the unfavourable group, a total of 23 events occurred; 7 in the standard arm, 16 in the experimental arm (1y-PFS 97.3% and 94.7% for standard and experimental arms, HR = 2.42 (CI: 1.5 - 4.36). The Trial Steering Committee declared futility according to previously set rules and considered that the risk of early relapse in non-irradiated patients with stage I-II cHL was significantly higher than standard combined modality treated patients even in the selected group with early PET negativity. Consequently the no RT arm was closed down and the study continued, with all patients receiving INRT, to investigate the secondary aim to determine the effect of escalation of therapy for patients with PET positive scans.

Both H10 and RAPID investigated the role of PET in applying a “response-adapted strategy” for early stage cHL but came to apparently opposite conclusions with regards to the possibility of omitting RT in PET negative patients. Final results with longer follow up of both studies will be required before firm conclusions can be made on this promising therapeutic strategy.

Two further ongoing studies from the German Hodgkin Study Group are also examining a response-guided approach in early stage disease, (HD16,HD17) with ABVD treatment for favourable disease (http://www.clinicaltrials.gov/ NCT00736320) or a combination of ABVD and escBEACOPP for unfavourable disease (http://www.clinicaltrials.gov/ NCT01356680). Both include a randomisation to a standard arm of combined modality treatment and an experimental arm where RT is

given to iPET positive patients and omitted for iPET negative patients. These studies are aiming to recruit 1100 patients each.

In advanced HL, trials are also testing whether it is safe to de-escalate treatment in good responders on interim PET as well as whether treatment outcomes can be improved in poorer responders. For patients receiving ABVD chemotherapy, de-escalation strategies on the basis of a negative interim PET include randomisation to ABVD vs AVD (RATHL study http://www.clinicaltrials.gov/ct2/show/NCT00678327), and IFRT vs no IFRT after completion of ABVD for patients with bulky disease (HD0801) http://www.clinicaltrials.gov/ct2 /NCT00784537. Escalation strategies on the basis of a positive interim PET include switching to BEACOPP (RATHL, HD0607 http://www.clinicaltrials.gov/ct2/show/NCT00795613, Rambam Health Care/RHC http://www.clinicaltrials.gov/ct2/show/NCT00392314, SWOGS0816 http://www.clinicaltrials.gov/ct2/show/NCT00822120) or high dose chemotherapy and autologous stem cell transplant (ASCT) (HD0801). For patients receiving escBEACOPP chemotherapy, de-escalation strategies include randomisation to escBEACOPP vs ABVD (AHL 11 study http://clinicaltrials.gov/ct2/show/NCT01358747) randomisation to escBEACOPP 4 cycles vs 8 cycles (HD18 http://www.clinicaltrials.gov/ct2/show/NCT00515554) and switching to ABVD (RHC). Escalation strategies include randomisation to escBEACOPP vs escBEACOPP and rituximab (HD18).

In aggressive NHL including Diffuse Large B cell Lymphoma (DLBCL), rapid reduction in FDG uptake during chemotherapy is associated with good prognosis (Figure 4). In studies involving 924 patients treated with CHOP or ACVBP ± rituximab, 2-5y PFS/EFS rates have been reported ranging between 73-86% for patients with CMR (Cashen et al., 2011; Haioun et al., 2005; Micallef et al., 2011;

Mikhaeel et al., 2005; Safar et al., 2012; Spaepen et al., 2002; D.-H. Yang et al., 2011; Yoo et al., 2011; P. L. Zinzani et al., 2011). Studies from 2005 and earlier reported poorer outcomes for patients with PET 'positive' scans with 2-5yPFS/EFS rates of 0-43% (Figure 5). Two recent studies also reported poor outcomes with 3-5y PFS rates of 18-29% (D.-H. Yang et al., 2011; P. L. Zinzani et al., 2011) but four other studies reported more favourable outcomes for patients with PET positive interim scans (Cashen et al., 2011; Micallef et al., 2011; Safar et al., 2012; Yoo et al., 2011) with 2-3y PFS rates of 47 – 66%. Possible reasons for this may be the improved prognosis in this disease with the addition of rituximab to standard treatment and inflammatory- induced uptake associated with the use of immunotherapy. In a disease where salvage treatment has become less effective since the introduction of rituximab, it is disappointing that early response assessment with PET appears to be less predictive of primary treatment failure than initially thought.

Methods to improve the predictive value of early PET include the use of quantitative approaches, such as measuring the reduction of the maximum SUV in the 'hottest' lesion before and during treatment referred to as 'ΔSUV' (Emmanuel Itti et al., 2009; Lin et al., 2007). Using receiver operating curves to define the best threshold to discriminate between good and poor treatment response groups, the French GELA group have published data to suggest that 'ΔSUV' predicts outcome better than visual assessment in DLBCL (Casasnovas et al., 2011; Emmanuel Itti et al., 2009; E. Itti et al., 2013; Lin et al., 2007). The optimal cut off varies according to when the PET scan is performed during treatment, as FDG uptake declines during chemotherapy, so a higher threshold is used at 4 cycles than 2 cycles (Emmanuel Itti et al., 2009). The ΔSUV is being used as a response measure in the PETAL study

(Duhrsen et al., 2009), with poor responders identified according to a ΔSUV ≥ 66% in the experimental arm randomised to receive escalated treatment with a B-ALL regimen in place of R-CHOP and good responders with ΔSUV <66% in the experimental arm receiving a total of 6 cycles of R-CHOP instead of the standard arm 8 cycles. Using the 66% cut-off, one retrospective study reported that ΔSUV was predictive of response in DLBCL (Safar et al., 2012) but another was unable to demonstrate an association of ΔSUV with PFS (Pregno et al., 2012). Other published studies have reported that ΔSUV is predictive of response but using different cut-offs for the ΔSUV of 76% and 92% respectively (Fuertes et al., 2013; D. H. Yang et al., 2013). The application of ΔSUV clearly requires further study and is dependent on proper standardisation of PET methods, including PET acquisition, cross-calibration of cameras and appropriate maintenance and quality control of imaging equipment prior to widespread use. Guidelines have been published regarding the best methods to perform PET for multicentre trials which are also recommended for best clinical practice and make such quantitative applications a realistic goal for future clinical use (Boellaard et al., 2010).

In Follicular Lymphoma with high tumour burden, interim PET is predictive of response to initial therapy, but the end of treatment scan appears to be a better predictor (Dupuis et al., 2012), perhaps because the response to chemotherapy is slower than in HL and DLBCL.

Currently there is insufficient evidence to change standard treatment based on the results of an interim PET-CT scan. Nonetheless an interim scan may be helpful to confirm that patients are responding to treatment and exclude progression of disease. PET-CT could replace CT in the interim setting if a mid-treatment scan is

indicated. The results of the PET-CT scan should always be interpreted in the context of the clinical situation and anticipated prognosis of disease, ideally in a multidisciplinary setting. If an interim scan shows a complete metabolic response, then there is no need to perform a treatment at the end of therapy if the clinical course is uncomplicated (M.; Hutchings et al., 2006; Strobel et al., 2007). In a study in 38 patients with HL and 30 with NHL, all patients with a complete response on interim PET had complete response on the end of treatment scan (Strobel et al., 2007).

What is the role of PET in end-of-treatment remission assessment?

There is a high predictive value for remission assessment using FDG-PET. In HL the NPV for ≥ 2-yPFS is 94-100% for patients treated with ABVD (Barnes et al., 2011; Cerci, Trindade, et al., 2010; Spaepen et al., 2001) with PPV of 91-92% (Cerci, Trindade, et al., 2010; Spaepen et al., 2001) for all stages but 46% in early stage non-bulky disease, again reflecting the good prognosis of patients in this group (Barnes et al., 2011).

In aggressive NHL including DLBCL, the NPV for end of treatment PET is also high, reported at 90-100% (Micallef et al., 2011; Pregno et al., 2012; Spaepen et al., 2001) but the PPV is lower and more variable, reported at 50-82% (Micallef et al., 2011; Pregno et al., 2012; Spaepen et al., 2001). The lower PPV is due to the non-specific nature of FDG as a tracer which is taken up in inflammation, such as may be seen following chemotherapy and radiotherapy treatment. For this reason, it is recommended that minimum periods between the end of treatment and scanning be left; at least 10 days for chemotherapy, at least 2 weeks after GCSF treatment and 3 months after radiotherapy (Boellaard et al., 2010). Biopsy confirmation of residual

disease is advisable before giving second-line treatment in both HL and aggressive NHL or if the clinical suspicion of residual disease is low, an interval scan may be preferred.

The improved remission assessment by PET led to its incorporation in the IWG criteria in 2007. In these criteria residual masses with negative FDG uptake were included in the Complete Response Category (Cheson et al., 2007). In a previous study in NHL this led to better discrimination of response categories and the removal of the category of CR 'unconfirmed' as patients were either reclassified as CR or PR according to FDG uptake (Juweid et al., 2005). Nowadays an end of treatment scan is usually performed in both HL and DLBCL to confirm remission (Figure 6) or to direct biopsy in the case of residual FDG uptake if further treatment is being considered (Figure 7).

FDG-PET may have a role in selecting patients with advanced HL who will benefit from the addition of consolidation RT after a full course of chemotherapy. In patients treated with escBEACOPP in the HD-15 study from the GHSG, 739 patients with residual masses >2.5cm were treated with radiotherapy according to the results of an end-of-treatment PET scan (Engert et al., 2012). 191 patients with PET positive residual masses received radiotherapy. Patients with negative residual masses were not treated with RT and had the same PFS as patients with complete radiological response and this strategy reduced the use of radiotherapy in advanced stage HL from 70% in HD12 to 11% in HD15. Radiotherapy is therefore not required in advanced stage HL patients treated with BEACOPP who achieve complete metabolic response after chemotherapy even in the presence of a residual mass. However it is important to note that these results may not apply to ABVD-treated patients or patients with early stage bulky disease where similar evidence is lacking.

In high tumor burden FL, two studies involving 122 and 116 patients respectively have recently reported inferior outcomes for patients according to PET-CT status at the end of treatment with rituximab and chemotherapy (Dupuis et al., 2012; Trotman et al., 2011). PFS rates of 33% and 51% for patients with residual uptake were reported compared to 71% and 87% for patients with CMR. OS rates were 78% and 88% for patients with residual uptake compared to 96% and 100% for patients with CMR. In the prospective study (Dupuis et al., 2012), the assessment of response at end treatment was predictive of response whereas the interim scan was not and this may reflect a slower metabolic response in this disease compared to HL and DLBCL. Maintenance rituximab was not given in one study (Dupuis et al., 2012) and in the other too few patients were included who had received maintenance rituximab to demonstrate a difference in PFS in patients according to maintenance therapy (Trotman et al., 2011). Whilst the role of PET in patients who receive maintenance rituximab may require further clarification, both studies found that response assessment with PET provided significant information with regard to prognosis where CT did not. In the prospective study, where a priori criteria were defined for PET reporting, a visual graded response assessment using the Deauville criteria were superior to 2007 IWG criteria (Dupuis et al., 2012). These data suggest that evaluating patients for trials with novel agents after initial treatment is best undertaken with PET-CT.

What is meant by a PET negative or positive scan?

PET scans are often referred to as ‘negative’ or ‘positive’ but FDG uptake represents a continuum, and the likelihood of malignancy in a lesion increases with the intensity of FDG uptake. The Guy’s and St Thomas’ group reported PET scans using 3 categories as ‘negative’ with ‘minimal residual uptake’ (MRU) or ‘positive’ (Hutchings

et al., 2005; Mikhaeel et al., 2005) and reported that the interpretation of MRU differed according to subtype and stage. For example, the PFS of patients with HL and aggressive NHL but limited stage at interim was the same or similar for patients with MRU as patients with negative scans, likely due to the effectiveness of treatment in these patients (Hutchings et al., 2005; Mikhaeel et al., 2005). Conversely MRU in aggressive NHL and advanced stage was predictive of poor prognosis (Mikhaeel et al., 2005). How FDG uptake is interpreted may also be time dependent. The IHP criteria which were recommended for end of treatment assessment, chose to use the mediastinum to define a 'negative' scan in lesions 2cm or larger but to use the adjacent background in smaller lesions (Juweid et al., 2007). However uptake higher than this, especially during the course of treatment is also associated with good prognosis in some patients (Andrea Gallamini et al., 2007). The need for criteria that could be adapted to the clinical context and take account of timing in relation to chemotherapy led to the development of a five point scale that might better reflect differing degrees of FDG uptake. This scale was recommended for use of reporting PET at the first international workshop on PET and lymphoma held in Deauville and is often referred to as the 'Deauville criteria'(Meignan et al., 2009) (Table 1). The five point scale has good interobserver agreement (Sally F. Barrington et al., 2010; Biggi et al., 2013; Dupuis et al., 2012; Furth et al., 2011; Le Roux et al., 2011) and appears to improve the PPV whilst maintaining the high NPV compared with IHP criteria (Dupuis et al., 2012; Le Roux et al., 2011; D.-H. Yang et al., 2011) if higher thresholds than the mediastinum are used to differentiate good from less good response, especially in the interim setting. The five point scale is in use in several response-adapted trials (RAPID, RATHL, HD0607,NCI, http://clinicaltrials.gov/ct2/ NCT00822120, IELSG37,

http://clinicaltrials.gov/ct2 /NCT01599559) with the advantage that the threshold of FDG uptake chosen may be higher for a trial involving escalation (to avoid risk of over-treatment) than a trial investigating de-escalation (to avoid under-treatment). Score 1,2,3 were used in the UK-led RATHL study to define a negative scan with patients with positive scans escalated to BEACOPP from ABVD. Score 1, 2 was however used to define a negative scan in the UK RAPID study where patients with early stage non-bulky disease and a negative scan were randomised to RT or no further treatment after 3 cycles of ABVD treatment. The use of the five-point scale relies on consistency in scanning conditions for serial scans and attention to patient preparation, scan acquisition and the quality control of imaging equipment as well as reporting methods is crucial (Boellaard et al., 2010).

What confounding factors may affect the use of FDG PET in lymphoma management?

FDG uptake is not specific for malignancy and uptake of the tracer occurs in inflammatory cells and infection which also have increased glucose metabolism. Indeed it has been suggested that one of the reasons why FDG is a good imaging biomarker in HL is its ability to detect inflammatory cells in the tumour microenvironment (A Gallamini, 2010). Clinicians need to be aware of potential confounding causes of increased FDG uptake which are well described (S. F. Barrington & O'Doherty, 2003; Cook et al., 2004) including intercurrent infection, inflammatory responses to treatment, synchronous malignancy and physiological variants such as thymic hyperplasia which may confound response assessment. It is especially important to question findings that are at variance with the clinical picture or where there is a 'mixed response' with apparent improvement in response in some areas of disease, but persistent FDG uptake or new lesions with increased

FDG uptake in others. These situations are best discussed in a multidisciplinary team setting.

What is the role in relapse and pre transplant assessment of PET?

PET can be used for restaging of patients at relapse as it is used in staging of de-novo lymphomas (Elstrom et al., 2008; Janikova et al., 2008; Schaefer et al., 2004). For patients undergoing autologous stem cell transplant (ASCT) for relapsed or refractory disease, a PET scan performed after salvage treatment has prognostic value with patients with a positive scan 3-7 times more likely to relapse or progress than patients with a negative scan. Series are mostly retrospective and used a variety of different salvage regimens (Terasawa et al., 2010), but all appear to support a role for PET in pre-transplant assessment with ASCT with PFS rates of 23-41% reported for patients with residual uptake and 71-82% for CMR patients (Devillier et al., 2012; Mocikova et al., 2011; Moskowitz et al., 2012; Smeltzer et al., 2011; Sucak et al., 2011). It remains controversial whether to offer transplantation to patients with less than CMR, with some series reporting successful outcomes in up to 40% of PET positive patients or to offer extended salvage therapy on the basis of a positive scan (Moskowitz et al., 2012). Perhaps the most important role for PET might be to act as a surrogate/early end-point in testing novel agents such as SGN-35 (Hutchings, 2011). Post-transplant assessment with PET has been reported as being predictive of PFS/OS in a small study with 43 patients with HL (Sucak et al., 2011) but not in another study of 68 patients with HL and NHL (Palmer et al., 2011). Prior to reduced intensity conditioning allogeneic transplant, one study in a mixed population of 80 patients (Dodero et al., 2010) reported that PET status was predictive of PFS and OS, whilst another in mixed population of 80 patients did not (Lambert et al., 2010). The authors of the latter study reported that PET detected

relapse post-allogeneic transplant earlier than CT and might be a useful tool during surveillance to select patients for donor lymphocyte infusion (DLI) and reported low incidence of graft versus host disease in patients who were PET +ve treated with DLI.

Is there a role for PET in surveillance of patients ?

Relapses are more likely to be detected in symptomatic patients than with surveillance imaging (Goldschmidt et al., 2011) especially for aggressive NHL. Surveillance scanning with PET however has been reported to detect unsuspected relapses in up to 10% of patients with HL and aggressive NHL in one series of 421 patients routinely scanned at 6,12,18,24 months then annually (Pier Luigi Zinzani et al., 2007). However lead-time bias is a problem in studies of patients undergoing surveillance imaging with earlier detection of disease leading to false impressions of longer survival time. As yet no data exist that demonstrates that earlier detection of disease improves outcomes for patients. Balanced against the desirability to detect early relapse, are the high rate of false positive rates reported with PET-CT scans. PPVs for PET-CT of only 21% and 23% were reported in two series of 52 patients with aggressive NHL in first-CR and 192 patients with HL respectively (Tarec El-Galaly et al., 2011; Lee et al., 2010) leading to unnecessary biopsies and patient anxiety. The cost to detect a single event was estimated at US$100 000 in the latter study (Lee et al., 2010). CT was similarly associated with a low PPV of 29% but considerably lower financial cost. The associated radiation burden also has to be taken into consideration. Currently there is no clear evidence to support surveillance imaging with PET-CT. However, it may be justified in very selected cases with high risk of relapse (T El-Galaly et al., 2013).

What is the Radiation dose typically associated with PET-CT?

The effective dose (ED) associated with a half-body PET scan is around 8mSv if the FDG activity administered is 400MBq, which is the diagnostic reference level used in the UK ("Administration of Radioactive Substances Advisory Committee Notes for Guidance," 2006,revised 2011). With recent advances with 3D imaging, time of flight and better image reconstruction algorithms, lower activities could be used or instead the activity may be kept the same, if faster imaging times are preferred. With the most up to date cameras, the effective dose could be reduced to 4-5 mSv (Boellaard et al., 2010) without a loss in image quality. If a low dose CT scan is used for localisation and attenuation correction, as part of PET-CT, with the parameters currently in use in our institution, the effective dose is 9mSv, but with more modern CT cameras would be approximately 7mSv, giving rise to a combined ED for PET-CT typically of 11-17mSv. This equates to 5-8 years of natural background radiation, which is 2.2mSv in the UK. The National Reference Dose Level for a full-dose contrast enhanced CT of the chest abdomen and pelvis of 940 mGycm (Shrimpton et al., 2005) corresponds to an Effective Dose of approximately 16 mSv ("The 2007 Recommendations of the International Commission on Radiological Protection," 2007) which is comparable to a PET-CT examination.

What about the use of PET-CT for T-cell Lymphomas?

Most reports related to staging and response assessment have included patients with B cell malignancy although some reports in patients with aggressive NHL have

included a few patients with T cell lymphomas. As a separate entity however, there are limited data on the use of FDG in patients with T cell and NK cell lymphomas. Most are FDG avid, with higher uptake in more aggressive subtypes but significantly lower uptake in cutaneous disease (Feeney et al., 2010; P. L. Zinzani, 2011). Patients with Mycosis Fungoides have higher FDG uptake in the presence of large cell transformation and it has been suggested that suspected transformation may be an indication for PET-CT, analogous to its use in FL (Feeney et al., 2010). Higher uptake is also seen in systemic manifestations of cutaneous lymphomas and a role in the detection of visceral involvement has been suggested as this alters management (Otero et al., 2009). Although PET also detects more lesions than CT in nodal and leukaemic variants of T cell lymphomas, this rarely affects management (Casulo et al., 2013). Interim assessment with FDG was reported to be predictive of PFS, but not OS, in one study of 50 patients with peripheral T cell lymphomas (Casulo et al., 2013), but not in another study involving 54 patients (Cahu et al., 2011); in the latter study the post-therapy scan also was not predictive of outcome. It is important not to extrapolate data relating to B cell lymphomas to patients with T cell lymphomas. As yet,there is no clearly defined role for FDG PET in this disease group with the possible exceptions of excluding visceral involvement with MF and suspected transformation. Because the numbers of patients are small, prospective multicentre trials are required. A UK study opened in 2012 investigating the response rate of CHOP versus gemcitabine, methylprednisolone and cisplatin and is prospectively measuring the complete metabolic response rate in patients with untreated T-cell lymphoma (http://www.clinicaltrials.gov/ct2/NCT01719835).

What other tracers are on the horizon for lymphoma?

There is growing interest in other tracers that might be more specific for malignancy than FDG and which will detect early changes in tumour behaviour in response to treatment. The use of 18F – Fluoro-L-Thymidine (FLT) has been explored in murine models of DLBCL (Graf et al., 2012), Mantle Cell Lymphoma (MCL)(Brepoels et al., 2009) Burkitts Lymphoma (BL)(Saint-Hubert et al., 2012) and FL (Buck et al., 2007). FLT follows the salvage pathway for DNA synthesis like thymidine and is phosphorylated by thymidine kinase 1 (TK1) in the cytosol and trapped intracellularly. TK1 is found in proliferating cells but not resting cells and activity increases just before and during the S Phase of the cell cycle when DNA synthesis occurs . FLT is thus a marker of proliferation.

In murine models, doxorubicin (Graf et al., 2012) and cyclophosphamide (Brepoels et al., 2009; Buck et al., 2007) induced falls in FLT as early as 48hours after treatment, associated with reduction in Ki67. In one study the fall in FLT was dose dependent (Graf et al., 2012) and in vitro cell lines, DNA flow cytometry revealed dose-dependent reductions in the S phase and increased G2 arrest with doxorubicin (Graf et al., 2012). FLT uptake remained steady thereafter. In contrast FDG uptake initially fell, but was then followed by a temporary rise (Graf et al., 2012) with doxorubicin and cyclophosphamide at 4-7 days (Brepoels et al., 2009) accompanied by an influx of inflammatory cells, then a fall followed by a further rise at day 12-14 due to tumour regrowth. This suggested that FLT might be less affected by the inflammatory response than FDG, although uptake of FLT has been reported in granulomatous conditions (Zhao et al., 2008) and reactive lymph nodes (Troost et al., 2007). In a BL model (Saint-Hubert et al., 2012), FDG fell rapidly with cyclophosphamide, with a marked increase in apoptosis measured with TUNEL, then levels reached a plateau at day 7-9 with increased inflammatory cells observed, but

no later rise in FDG levels was seen. FLT fell less markedly and later after treatment than FDG, with a small reduction in Ki67 observed. Delayed response with FLT was attributed to increased DNA repair and a rise in TK1 in response to cyclophosphamide induced DNA crosslinks early after administration (Saint-Hubert et al., 2012) and the authors suggested contrary to their earlier work using a MCL model, that in BL, FDG might be a better tracer to assess response than FLT. With Temsirolimus, an mTOR inhibitor, rapid and marked reductions in both FLT and FDG were reported (Brepoels et al., 2009; Saint-Hubert et al., 2012)with a rise in FDG at day 4 in one study but not the other and slow rises in both tracers towards day 14 with tumour regrowth. In the MCL model a temporary rise in FLT occurred at day 7, accompanied by a rise in cyclin D1 levels. Cyclin D1 induces cell cycle transition from the G1 to the S phase and is one of the targets controlled by mTOR, which regulates cellular proliferation and is over-expressed in MCL due to the translocation t(11;14). This suggests that at day 7, the tumour had overcome the effects of the mTOR inhibitor. To better understand when to assess response relies on understanding the complex interactions between the tracer behaviour and the tumour biology and mechanisms of drug action(s).

In a study of 22 patients with high-grade NHL (Herrmann et al., 2007), reductions in FLT were reported at day 2 and day 7 after treatment with CHOP but not with single-agent rituximab. The only patient who progressed on treatment demonstrated high persistent FLT uptake and there were significant differences in patients who achieved CR compared to PR. There were insufficient non-responding patients to determine any effect on responders vs. non-responders. FLT has high uptake in bone marrow and liver and may be more limited to assess disease at these sites.

Uptake with FLT is lower than FDG at baseline in lymphoma (Brepoels et al., 2009) however baseline mean FLT has been reported to be significantly lower in patients with aggressive NHL in one study who achieved CR (n=55) compared to patients with no-CR (n=7) and to correlate with the IPI (Herrmann et al., 2011). In 48 lymphoma patients with residual masses post chemotherapy, 31 of whom had radiotherapy, FDG was a better predictor of overall survival than FLT, although patients who were FDG positive and FLT positive had a worse outcome than those that were FDG positive and FLT negative (Kasper et al., 2007). Perhaps proliferation effects in lymphoma are less important at this time point and interest will continue to focus on early response assessment with FLT.

Conclusion

The indications and benefits of using PET-CT in the modern management of lymphoma are summarised in Table 2.

PET-CT is routinely used in the staging of patients with HL and DLBCL and early-stage FL because it alters stage in a proportion of patients, but also because a baseline scan is required for accurate subsequent response assessment. In FL and MF, PET-CT may be used to direct biopsy in suspected transformation. There is strong evidence to support a role for interim assessment with PET-CT in HL. In DLBCL, iPET has a high negative predictive value but the positive predictive value is lower in patients receiving R-chemotherapy. The role of response-adapted treatment in both these diseases is being explored in multicentre international trials. Preliminary reports from RAPID and H10 studies are emerging on the role of iPET in selecting patients who may not need RT in early stage cHL but final reports of these studies are awaited with interest. Post-treatment assessment with PET-CT is more

accurate than CT for HL, DLBCL and FL. Complete metabolic response is highly indicative of remission and HL patients treated with BEACOPP with PET-negative residual masses do not require radiotherapy. Residual uptake following ABVD or R-chemotherapy requires biopsy or interval scanning. PET-CT prior to ASCT is a strong predictor of outcome and may have a role in the evaluation of novel agents in this setting. Data relating to the use of FDG in T-cell lymphomas is limited and further studies are required. In cutaneous T-cell lymphoma, PET does not have a routine role in staging or response assessment with the exception of the detection of visceral involvement in MF.

Figures

Figure 1 Coronal slices with low-dose CT, PET and fused images are shown of a patient with HL. Note the PET and fused images are displayed to a maximum SUV of 10. This is the fixed scale used for reporting at our Centre.

Figure 2 Coronal slices (low-dose CT, PET and fused images) show focal uptake in the spleen (arrowed) which is not enlarged and has normal appearances on CT.

Figure 3 Sagittal slices (low-dose CT, PET and fused images) are shown of a patient with DLBCL and marrow involvement, pre (A) and post treatment (B). Note how some vertebrae eg T12 with increased uptake become photopaenic with ablation of marrow, whilst other vertebrae with normal uptake at baseline have increased uptake relative to baseline due to the effects of chemotherapy. The images demonstrate a 'mirror' effect.

Figure 4 Coronal slices (low-dose CT, PET and fused images) are shown of a patient with DLBCL with extensive nodal and pleural disease at staging (A) but with a complete metabolic response after 2 cycles of R-CHOP with a residual pleural effusion (B).

Figure 5 Coronal slices (low-dose CT, PET and fused images) are shown of a patient with DLBCL with disease in the left axilla (A) which persists during treatment with 2 cycles of R-CHOP (B).

Figure 6 Axial slices (low-dose CT, PET and fused images) are shown of a patient with HL with high grade uptake in a mediastinal mass pre treatment (A) and a complete metabolic response post-treatment (B).

Figure 7 Axial slices (low-dose CT, PET and fused images) are shown of a patient with HL with high grade uptake in a mediastinal mass pre treatment (A) with a small focus of residual uptake post-treatment (B) concerning for treatment failure, requiring biopsy.

Figure 8 Coronal slices (low-dose CT, PET and fused images) are shown of a patient with sarcoid-like reaction with a typical distribution of FDG uptake in nodes in the mediastinum and within the lung.

Table 1 – The Five point scale (5PS/Deauville criteria)
The 5PS scores the most intense residual uptake in a site of initial disease as: 1. no uptake 2. uptake ≤ mediastinum ** 3. uptake > mediastinum but ≤ liver 4. uptake moderately higher than liver 5. uptake markedly higher than liver and/or new lesions X new areas of uptake unlikely to be related to lymphoma ***NOTE if MBP ≥ liver activity, the uptake within lesions should be compared with liver (uptake lesion < liver is score 2; lesion = liver is score 3)***

Table 2 Indications and Benefits for using PET-CT in Lymphomas

Indication/s	Benefit/s
PRE-TREATMENT	
Staging of patients with FDG-avid Lymphomas	Increased staging accuracy Improved treatment selection Improved accuracy of response assessment
To direct biopsy in suspected transformation of FL	Improved disease characterisation and treatment selection
Assessment of bone marrow involvement in HL and DLBCL	Improved accuracy than biopsy Avoidance of morbidity associated with BMB
Radiotherapy planning for patients with HL and DLBCL	More refined definition of radiotherapy volume + less irradiation of normal tissue. Essential for techniques less than IFRT
DURING TREATMENT	
Mid-treatment imaging to monitor response in HL and DLBCL	More accurate monitoring of response than mid-treatment CT

	(and earlier assessment) No evidence to modify treatment as yet, but useful to detect poor or no response early
POST-TREATMENT	
End of treatment assessment in HL DLBCL and FL (unless patients have had mid-treatment imaging showing complete metabolic response) to confirm disease remission or to direct biopsy if residual disease is suspected	More accurate assessment of remission than CT especially in cases of CRu or PR Part of IWG criteria Possible role to select patients for consolidation RT (e.g. advanced stage cHL after BEACOPP)
RELAPSE	
Pre-transplant assessment in patients undergoing ASCT with HL or DLBCL	More accurate and prognostic than CT

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When should FDG-PET be used in the modern management of lymphoma?

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Summary

Positron Emission Tomography (PET) is a functional imaging technique which combined with CT (PET-CT) is increasingly used in lymphoma. Most subtypes accumulate Fluorodeoxyglucose (FDG) and the increased sensitivity of PET-CT, especially for extranodal disease, compared to CT, makes PET-CT an attractive staging tool. The availability of a staging PET-CT scan also improves the accuracy of subsequent response assessment. 'Interim' PET-CT can be used to assess early response and end-of-treatment PET-CT to assess remission. Clinical trials are currently seeking to establish whether the predictive value of PET-CT can be successfully used to guide individual treatment to reduce toxicity and/or to improve outcomes. Standardised methods for performing and reporting PET have been developed in the context of trials. The role of PET in transplantation selection is evolving as PET appears to be more accurate and prognostic than CT. The role of FDG PET-CT throughout the management course in patients with lymphoma is explored in this review with areas discussed that may limit the use of PET-CT imaging which clinicians should be familiar with to inform practice. (174 words)

Keywords: Positron Emission Tomography, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Clinical Trials, Imaging.

What is PET?

Positron Emission Tomography (PET) images physiological processes by detecting radioactive emissions from Positron Emitting radioisotopes or 'tracers' injected into a patient. The most commonly used tracer is 18F-Fluorodeoxyglucose (FDG) which is a glucose analogue which has increased uptake in cancer due to enhanced glucose transport, turnover and trapping. Other processes with increased glycolysis, such as infection and inflammation have increased FDG uptake, but often to a lesser degree than malignancy.

Modern PET cameras are now combined with a CT scanner, enabling functional and anatomical information to be obtained together. CT and PET can be viewed separately, side-by-side and 'fused' with the PET scan overlaid on the CT in colour.

PET scans are usually reported using visual assessment. The intensity and locations of FDG-avid disease are described and distinguished from areas with high physiological uptake, such as the brain and the urinary system, where FDG is excreted. Scans are usually displayed scaled according to the standardised uptake value (SUV) which is the activity of the tracer, corrected for patient weight and the administered radioactivity (Figure 1). The use of a fixed SUV display aids consistency of reporting, by enabling uptake to be to be assessed at successive time-points within the same patient during treatment and by reducing the effect of weight on uptake across different patients. SUV measures may be used to quantify uptake; most commonly the 'maximum' (SUVmax) is used to describe intensity. The CT is used to localise the PET abnormalities and any additional findings on CT reported.

The CT may be acquired at full dose with intravenous and/or bowel contrast, similar to a 'stand-alone' CT but must be acquired during normal breathing rather than full inspiration, to fuse with the PET which is acquired in steps over 15-25 minutes. Alternatively the CT may be acquired at lower dose, which is more common practice for PET-CT imaging. Then the CT is used a) to measure how Xrays are attenuated in the patient and apply a correction to the FDG images to give a truer appreciation of tracer distribution and b) to accurately localise sites of uptake.

Which Lymphomas can be imaged with PET ?

Most Lymphomas are FDG-avid. In a series of 766 patients imaged with lymphoma, 100% of Hodgkin lymphoma (HL), 97% of Diffuse Large B cell Lymphoma (DLBCL) and 95% of Follicular Lymphomas (FL) were FDG-avid (Weiler-Sagie et al., 2010). Less common aggressive subtypes were also universally FDG-avid including Burkitt lymphoma, Mantle Cell lymphoma and aggressive T-cell lymphomas. More variable avidity has been reported for small lymphocytic lymphoma (50-83%), extranodal marginal zone lymphoma (54-67%), and lymphomas that involve the skin (Elstrom et al., 2003; Tsukamoto et al., 2007; Weiler-Sagie et al., 2010).

Aggressive lymphomas mostly have higher uptake than indolent lymphomas. In a study of 97 patients with NHL, although some patients with indolent and aggressive disease had SUVs in the lower range, all patients with indolent lymphoma had SUVmax <13 (Schoder et al., 2005). Using an SUVmax ≥ 10 distinguished aggressive from indolent disease with 81% specificity and 71% sensitivity. SUVmax also correlates with proliferation, measured by the Ki-67 index in lymph node and extranodal biopsies obtained from patients with indolent and aggressive lymphomas (Watanabe et al., 2010).

This suggests that FDG-PET may be used in patients with suspected transformation to direct biopsy.

What is the added value of PET for staging?

PET is more sensitive and specific than CT (Schaefer et al., 2004) because abnormal FDG uptake may be observed in normal-sized nodes and seen without changes in organ architecture (Figure 2). Equally, slightly enlarged nodes which may be reactive will not accumulate FDG. Upstaging occurs more commonly than downstaging, although both occur. Extranodal disease is more often identified with PET than CT within the bone and bone marrow (Figure 3), liver and spleen (Raanani et al., 2006) and occasionally in the peritoneum. Small lung nodules may not be resolved by PET but these are usually visible on the accompanying CT. Cutaneous lesions are less FDG-avid than extracutaneous disease and PET may have a role to detect extracutaneous disease in patients with Mycosis Fungoides, which confers a worse prognosis (Feeney et al., 2010; Otero et al., 2009). The brain has high physiological FDG uptake which limits the ability to detect metastatic disease in other diseases (Larcos & Maisey, 1996) but intracerebral lymphoma is highly avid and PET has been used to distinguish toxoplasmosis from intracerebral lymphoma in HIV patients (O'Doherty et al., 1997). Nonetheless, leptomeningeal disease which is diffuse and may be low volume is difficult to assess and MR is the investigation of choice for initial assessment of CNS lymphoma.

The presence of a baseline scan improves the accuracy of subsequent response assessment and improves reporter agreement (Meignan, Itti, et al., 2009) . The availability of a baseline scan has been reported to affect the classification of metabolic response in 19-34% of lymphoma patients. (S.F. Barrington et al., 2011;

Quarles van Ufford et al., 2010). Baseline PET is also important for planning of radiotherapy, especially using newer techniques treating smaller volumes than traditional involved-field radiotherapy (IFRT). It is recommended that the use of 'involved-site' radiotherapy (Specht et al., 2013) and 'involved-node' radiotherapy (INRT) (Girinsky et al., 2007) should ideally be based on staging PET-CT rather than CT alone.

The frequency of management change from using PET-CT for staging ranges from approximately 10 - 50%, but is typically around 15% (M. Hutchings et al., 2006; Naumann et al., 2004; Partridge et al., 2000; Pelosi et al., 2008; Raanani et al., 2006; Wirth et al., 2008). In patients with 'apparently' limited-stage Follicular Lymphoma on CT, PET may have an important impact because up to 60% (Karam et al., 2006; Luminari et al., 2013; Wirth et al., 2008) will have more advanced disease demonstrated. The upstaging has significant implications on the choice of therapy. Patients with limited-stage FL are commonly treated with radiotherapy alone however patients with more advanced disease usually require systemic treatment.

The presence of focal uptake in the bone marrow on PET-CT is more sensitive for bone marrow involvement than bone marrow biopsy in HL (T. C. El-Galaly et al., 2012) and aggressive NHL (Berthet et al., 2013; Khan et al., 2013). Diffuse homogenous FDG uptake may be seen with reactive hyperplasia in the marrow, especially in HL and does not necessarily indicate involvement. In a study in 454 patients with HL, no patients with stage I or II disease on PET-CT were upstaged by biopsy. Eighty-two patients had marrow involvement by PET, 27 by biopsy. Of these 27 patients, 22 had extranodal disease elsewhere on PET, the remaining five were upstaged from stage 3 to 4 by biopsy but this did not change treatment. Thus

biopsy did not alter management in a single patient (T. C. El-Galaly et al., 2012) suggesting that staging PET-CT may be used in preference (B.D. Cheson, 2012).

In aggressive NHL, small volume disease, typically ≤ 10% marrow involvement or coexistent low grade lymphoma (Paone et al., 2009) may be missed by PET but this has not been shown to affect prognosis or treatment (Campbell et al., 2006; Ghesquieres et al., 2006; Sehn et al., 2011). In a study of 130 patients with DLBCL, 33 patients had marrow involvement on PET, 14 on biopsy (Khan et al., 2013). No case was classified as stage 4 based on biopsy alone. Patients with PET and biopsy evidence of marrow involvement had worse prognosis than the rest of the study population but these patients frequently had other adverse factors predictive of high risk disease. Two patients with marrow involvement on biopsy had normal marrow appearances on PET with <10% of the marrow involved. In a further study of 133 patients with DLBCL, marrow involvement with PET and the IPI were independent predictors of PFS, whereas bone marrow biopsy was not (Berthet et al., 2013). This also suggests a restricted role for bone marrow biopsy in DLBCL patients staged by PET-CT.

PET-CT is less sensitive than biopsy for marrow involvement in indolent lymphomas, which is frequently diffuse, can be small volume and have low grade FDG uptake. The sensitivity was reported as 46% in indolent lymphomas in a recent meta-analysis (Chen et al., 2011). Biopsy with histological examination including immunohistochemistry and testing for clonality remains the gold standard in indolent lymphomas.

Is contrast enhanced CT necessary in addition to PET (CT) ?

PET-CT is routinely used for staging patients but whether a full-dose contrast-enhanced CT is required in addition to the low-dose non-contrast CT that is usually performed as part of the PET-CT examination is less clear. Several studies have reported that PET with low-dose CT demonstrated more lesions than contrast-enhanced CT alone (Elstrom et al., 2008; Raanani et al., 2006; Schaefer et al., 2004). The use of contrast-enhanced CT did not alter stage nor change management in three series (Elstrom et al., 2008; Gollub et al., 2007; Pinilla et al., 2011) but in one series, contrast-enhanced CT altered stage in 8/68 patients with NHL and 4/35 patients with HL, affecting management in nine (Raanani et al., 2006) however the details of management change were not reported. In two further publications (Pinilla et al., 2011), the use of contrast was felt to improve disease detection in the small bowel and pancreas in two patients, affecting management in one (Schaefer et al., 2004) .

Pragmatically, many patients will have a contrast-enhanced CT scan performed prior to PET-CT, then a low-dose CT will suffice for PET-CT. If PET-CT is performed first, contrast-enhanced CT may be preferred in patients likely to undergo radiotherapy, preferably in the anticipated treatment position. For clinical trials, contrast-enhanced CT is necessary if accurate size measurements are required, and would be more convenient performed during a single PET-CT scanning session. For other patients, whether the additional radiation incurred with a full dose contrast-enhanced CT is justified should be considered. Additional findings reported with contrast-enhanced CT were due to using contrast rather than the increased X-ray dose and there may be a role for regional low-dose CT with contrast after PET-CT. If a contrast-

enhanced CT is performed at staging and there is no additional benefit, subsequent examinations should be performed at lower dose.

What is the role of PET in early response assessment?

Metabolic changes precede changes in tumour size, which enables response to be assessed earlier during treatment with PET than CT. Rapid reduction in FDG uptake during chemotherapy is associated with a good prognosis in patients with HL and persistent FDG uptake with a poor prognosis in advanced HL patients. The group at Guy's and St Thomas' reported in 2005 a retrospective analysis of 85 HL patients where PFS and OS were significantly different according to whether the PET scan performed after 2 or 3 cycles of chemotherapy was reported as 'negative', showing 'minimal residual uptake' or 'positive'(Hutchings et al., 2005). Patients with a negative scan or minimal residual uptake had 5y-PFS rates of 92% compared with 39% for patients with a positive scan. This was followed by further reports after 2 cycles of chemotherapy in HL, involving 1066 patients treated with ABVD (Biggi et al., 2013; Cerci, Pracchia, et al., 2010; Andrea Gallamini et al., 2007; M.; Hutchings et al., 2006; P. L. Zinzani et al., 2012). These studies also reported ≥2y PFS rates of 90-96% for patients with complete metabolic response (CMR) and PFS rates of 0%, 13%, 28%, 28%, 53% respectively for patients with positive scans, with poorer outcomes in advanced disease (Andrea Gallamini et al., 2007; M.; Hutchings et al., 2006). PET was a better predictor than the IPS (Andrea Gallamini et al., 2007). A study reporting outcomes in 96 patients with early stage non-bulky HL (Barnes et al., 2011) found no difference in PFS according to early or 'interim' PET (iPET) although the end-of-treatment PET was predictive of outcome, probably due to the excellent prognosis of this patient group and the effect of radiotherapy. Radiotherapy was given to 56% of patients in the study and used more often in patients with positive

than negative interim scans (88% v 54%). A report in 69 patients treated with BEACOPP reported 4y-PFS of 98% and 78% for patients with positive and negative iPET scans respectively (p=0.016)(Markova et al., 2012). The ability of interim PET to predict prognosis early in treatment is clearly influenced by its timing in relation to chemotherapy, the disease stage and the treatment regimen. At present, iPET at 2-3 cycles has been shown to be predictive of outcome in advanced stage, ABVD-treated patients but extrapolation of these results to BEACOPP-treated patients is not advisable.

These studies highlighted the potential to use PET to tailor treatment for the individual according to their response during chemotherapy. The good prognosis associated with negative iPET has led to the question whether short-course chemotherapy without radiotherapy is an option for patients with early-stage favourable HL who have a negative iPET scan during ABVD treatment rather than combined modality treatment.

The UK National Cancer Research Institute study group recently presented the first results of the RAPID trial involving 602 patients with HL who had a PET scan performed after 3 cycles of ABVD (Radford et al., 2012). The study included non-bulky stage I & IIA disease and was designed to exclude a difference of ≥7% between radiotherapy and no further treatment. Patients with a complete metabolic response (defined as score 1 & 2 using a 5-point scale) were randomised to receive IFRT or no treatment, whilst patients with a positive scan (score 3-5) received one further cycle of ABVD and 30Gy IFRT. 3y-PFS in 420 randomised patients with PET negative scans was 93.8% in the group receiving RT and 90.7% in the group receiving no further treatment, (risk difference -2.9%, 95%CI -10.7 to 1.4%). 3-year OS was 97.0% in the RT group versus 99.5% in the no further treatment group. PFS

and OS in the PET positive group was 85.9 % and 93.9% respectively with a median follow-up of 46 months. These preliminary data suggest that patients with iPET score 1-2 after three ABVD cycles have excellent prognosis with three ABVD alone but longer follow-up is required to assess the trade-off between disease-control and risks of late treatment-effects. This is especially relevant in patients for whom the risks associated with radiotherapy may be lower, such as patients >35 years and when irradiation of female breast tissue and/or the heart is not required.

The H10 study from the EORTC is ongoing and was designed with randomisation to experimental or standard arms. Treatment in the standard arm is 3 or 4 cycles of ABVD for favourable (F) or unfavourable (U) disease respectively followed by INRT 30Gy + 6Gy boost to residual lesions. The experimental arm adopted a PET-based strategy with 2 cycles of ABVD followed by PET. If PET showed CMR, patients received 3 (F) or 4 (U) cycles of ABVD and no radiotherapy. If PET was positive, patients received 2 cycles of escBEACOPP. The first interim analysis of 1137 patients was recently presented (Andre et al., 2012). In the favourable group, ten events occurred; 1 in the standard arm, 9 in the experimental arm (1y-PFS 100% and 94.9% for standard and experimental arms respectively, HR 9.36 (CI : 2.45 – 35.73)). In the unfavourable group, 23 events occurred; 7 in the standard arm, 16 in the experimental arm (1y-PFS 97.3% and 94.7% for standard and experimental arms, HR = 2.42 (CI: 1.5 - 4.36)). The Steering Committee declared futility according to previously set rules and considered that the risk of early relapse for non-irradiated patients with stage I-II cHL was significantly higher than for patients receiving standard combined modality, even for patients with early PET negativity. Consequently the no radiotherapy arm was closed but the study continued, to

investigate the secondary aim to determine the effect of treatment escalation for patients with PET positive scans.

Both H10 and RAPID investigated the application of a PET “response-adapted strategy” for early stage classicalHL but apparently came to opposite conclusions regarding the possibility of omitting radiotherapy in patients with PET-negative scans. Final results with longer follow-up of both studies will be required before firm conclusions can be made on this promising therapeutic strategy.

Two further studies from the German Hodgkin Study Group are examining a response-guided approach in early-stage disease, (HD16, HD17) with ABVD treatment for favourable disease or a combination of ABVD and escBEACOPP for unfavourable disease. (All study identifiers are listed in table 1). Both include randomisation to a standard arm of combined modality treatment versus an experimental arm where radiotherapy is given to patients with iPET positive scans but omitted for patients with iPET negative scans.

In advanced HL, trials are also testing whether treatment outcomes can be improved in poor responders on iPET as well as safely de-escalated in good responders.

For patients receiving ABVD chemotherapy:

De-escalation strategies on the basis of a negative iPET include

- randomisation to ABVD vs AVD (RATHL),
- IFRT vs. no IFRT after ABVD for patients with bulky disease (HD0801).

Escalation strategies on the basis of a positive interim PET include switching to

- BEACOPP (RATHL, HD0607, Rambam Health Care/RHC, SWOGS0816)

- high dose chemotherapy and autologous stem cell transplant (ASCT) (HD0801).

For patients receiving escBEACOPP chemotherapy:

De-escalation strategies on the basis of a negative iPET include

- randomisation to escBEACOPP vs ABVD (AHL 11)
- randomisation to 4 vs. 8 cycles escBEACOPP (HD18)
- switching to ABVD (RHC).

Escalation strategies include randomisation to escBEACOPP vs escBEACOPP and rituximab (HD18).

In aggressive NHL including Diffuse Large B cell Lymphoma (DLBCL), rapid reduction in FDG during chemotherapy is associated with good prognosis. In studies involving 924 patients treated with CHOP or ACVBP ± rituximab and scanned after 2-4 cycles of treatment, 2-5y PFS/EFS rates have been reported between 73-86% for patients with CMR (Cashen et al., 2011; Haioun et al., 2005; Micallef et al., 2011; Mikhaeel et al., 2005; Safar et al., 2012; Spaepen et al., 2002; D.-H. Yang et al., 2011; Yoo et al., 2011; P. L. Zinzani et al., 2011). Studies from 2005 and earlier reported poorer outcomes for patients with PET 'positive' scans with 2-5y PFS/EFS rates of 0-43% (Haioun et al., 2005; Mikhaeel et al., 2005; Spaepen et al., 2002). Two recent studies also reported poor outcomes with 3-5y PFS rates of 18-29% (D.-H. Yang et al., 2011; P. L. Zinzani et al., 2011) but four other studies reported more favourable outcomes for patients with iPET positive scans (Cashen et al., 2011; Micallef et al., 2011; Safar et al., 2012; Yoo et al., 2011) with 2-3y PFS rates of 47 – 66%. Possible reasons may be the improved prognosis in DLBCL with rituximab treatment and the inflammatory-induced FDG uptake associated with rituximab. In

this disease where salvage treatment has become less effective since the introduction of rituximab, it is disappointing that early response assessment with PET appears to be less predictive of primary treatment failure than initially thought.

Methods to improve the predictive value of early PET include the use of quantitative approaches, such as measuring the reduction of the maximum SUV in the 'hottest' lesion before and during treatment, referred to as 'ΔSUV' (Emmanuel Itti et al., 2009; Lin et al., 2007). Using receiver operating curves to define the best threshold to discriminate between good and poor treatment response groups, the French GELA group have published data to suggest that 'ΔSUV' predicts outcome better than visual assessment in DLBCL (Casasnovas et al., 2011; Emmanuel Itti et al., 2009; E. Itti et al., 2013; Lin et al., 2007). The optimal cut-off varies according to when the scan is performed during treatment, as FDG uptake declines during chemotherapy, so a higher threshold of 70% is used at 4 cycles to define response (Emmanuel Itti et al., 2009). The ΔSUV is being used to measure response in the PETAL study (Duhrsen et al., 2009). After 2 cycles of R-CHOP, poor responders with ΔSUV < 66% are randomised to receive either escalated treatment with 6 cycles of a B-ALL regimen or 6 R-CHOP. Good responders with ΔSUV ≥66% are randomised to receive a further 4 or 6 cycles of R-CHOP. Using the 66% cut-off, one retrospective study reported that ΔSUV was predictive of response in DLBCL (Safar et al., 2012) but another was unable to demonstrate an association between ΔSUV with PFS (Pregno et al., 2012). Other published studies have reported that ΔSUV is predictive of response but using different cut-offs for the ΔSUV of 76% and 92% respectively (Fuertes et al., 2013; D. H. Yang et al., 2013). The application of ΔSUV clearly requires further study and is dependent on proper standardisation of PET methods,

including scan acquisition, cross-calibration of cameras and appropriate maintenance and quality control of imaging equipment prior to widespread use. Guidelines have been published regarding the best methods to perform PET for multicentre trials which are also recommended for best clinical practice and make such quantitative applications a realistic future goal (Boellaard et al., 2010).

In Follicular Lymphoma with high tumour burden, interim PET is predictive of response to initial therapy, but the end of treatment scan appears to be a better predictor (Dupuis et al., 2012), perhaps because the response to chemotherapy is slower than in HL and DLBCL.

Currently there is insufficient evidence to change standard treatment based on the results of an interim PET-CT scan. Nonetheless an interim scan may be helpful to confirm that patients are responding to treatment and exclude progression of disease. PET-CT could replace CT in the interim setting if a mid-treatment scan is indicated. The results of the PET-CT scan should always be interpreted in the context of the clinical situation and anticipated prognosis of disease, ideally in a multidisciplinary setting. If an interim scan shows a complete metabolic response, then there is no need to perform a treatment at the end of therapy if the clinical course is uncomplicated (M.; Hutchings et al., 2006; Strobel et al., 2007).

What is the role of PET in end-of-treatment remission assessment?

There is a high predictive value for remission assessment using FDG-PET. In HL the NPV for ≥ 2-yPFS is 94-100% for patients treated with ABVD (Barnes et al., 2011; Cerci, Trindade, et al., 2010; Spaepen et al., 2001) with PPV of 91-92% (Cerci, Trindade, et al., 2010; Spaepen et al., 2001) for all stages but 46% in early

stage non-bulky disease, again reflecting the good prognosis of patients in this group (Barnes et al., 2011).

In aggressive NHL including DLBCL, the NPV for end of treatment PET is also high, reported at 90-100% (Micallef et al., 2011; Pregno et al., 2012; Spaepen et al., 2001) but the PPV is lower and more variable, reported at 50-82% (Micallef et al., 2011; Pregno et al., 2012; Spaepen et al., 2001). The lower PPV can be attributed to the non-specific nature of FDG as a tracer which is taken up in inflammation, such as may be seen following chemotherapy and radiotherapy treatment. For this reason, it is recommended that scanning takes place >10 days after chemotherapy, two weeks after GCSF treatment and three months after radiotherapy (Boellaard et al., 2010). Biopsy confirmation of suspected residual disease is advisable before giving second-line treatment in HL and aggressive NHL, however if biopsy is difficult or is negative but the clinical suspicion of residual disease is high, additional treatment may be considered in carefully selected cases. If the clinical suspicion of residual disease is low, an alternative approach would be to perform an interval scan.

The improved remission assessment using PET led to its incorporation in the International Working Group (IWG) criteria in 2007. Residual masses with negative FDG uptake were included in the Complete Response Category (Bruce D. Cheson et al., 2007). In a previous study in NHL this led to better discrimination of response categories and the removal of the category of CR 'unconfirmed' as patients were reclassified as CR or PR according to FDG uptake (Juweid et al., 2005). Nowadays an end-of-treatment scan is usually performed in HL and DLBCL to confirm remission or to direct biopsy in the case of residual FDG uptake if further treatment is being considered.

FDG-PET may have a role in selecting patients with advanced HL who will benefit from consolidation radiotherapy after a full course of chemotherapy. In patients treated with escBEACOPP in the HD-15 study, 739 patients with residual masses >2.5cm were treated with radiotherapy according to the results of an end-of-treatment PET scan (Engert et al., 2012). 191 patients with PET positive residual masses received radiotherapy. Patients with negative residual masses were not treated with radiotherapy and had the same PFS as patients with complete radiological response. This strategy reduced the use of radiotherapy in advanced-stage HL from 70% in HD12 to 11% in HD15. Radiotherapy is therefore not required in advanced-stage HL patients treated with BEACOPP who achieve complete metabolic response after chemotherapy, even in the presence of a residual mass. However it is important to note that these results may not apply to ABVD-treated patients or patients with early stage bulky disease where similar evidence is lacking.

In high tumor burden FL, end-of-treatment PET appears to be a good predictor of outcome. Two studies involving 122 and 116 patients respectively have recently reported inferior outcomes for patients according to PET-CT after rituximab and chemotherapy treatment (Dupuis et al., 2012; Trotman et al., 2011). PFS rates of 33% and 51% for patients with residual uptake were reported compared to 71% and 87% for patients with CMR. OS rates were 78% and 88% for patients with residual uptake compared to 96% and 100% for patients with CMR. Maintenance rituximab was not given in one study (Dupuis et al., 2012) and in the other too few patients were included who had received maintenance rituximab to demonstrate a difference in PFS according to maintenance therapy (Trotman et al., 2011). Whilst the role of PET in patients who receive maintenance rituximab may require further clarification, both studies found that response assessment with PET was prognostic whilst CT

was not. In the prospective study, where *a priori* criteria were defined for PET reporting, a visual graded response assessment using the Deauville criteria were superior to 2007 IWG criteria (Dupuis et al., 2012). These data suggest that evaluating patients for trials with novel agents after initial treatment is best undertaken with PET-CT.

What is meant by a PET negative or positive scan?

PET scans are often referred to as 'negative' or 'positive' but FDG uptake represents a continuum. The likelihood of malignancy increases with the intensity of FDG uptake. The Guy's and St Thomas' group reported PET scans using 3 categories as 'negative' with 'minimal residual uptake' or 'positive' (Hutchings et al., 2005; Mikhaeel et al., 2005) and reported that the interpretation of minimal residual uptake differed according to subtype and stage. For example, the PFS of patients with limited stage HL and aggressive NHL was similar at interim for patients with no uptake and patients with minimal residual uptake, likely due to the effectiveness of treatment (Hutchings et al., 2005; Mikhaeel et al., 2005). Conversely minimal residual uptake in advanced-stage aggressive NHL was predictive of poor prognosis (Mikhaeel et al., 2005). The interpretation of FDG uptake is also time dependent. The International Harmonisation Project (IHP) criteria which were recommended for end-of-treatment assessment, chose to use the mediastinum to define a 'negative' scan in lesions ≥ 2cm or the adjacent background in smaller lesions (Juweid et al., 2007). However uptake higher than this is often associated with good prognosis, especially during the course of treatment (Andrea Gallamini et al., 2007). The need for criteria that could be interpreted according to clinical context and timing in relation to chemotherapy led to the development of a five-point scale which may better reflect differing degrees of FDG uptake. This scale was recommended for reporting PET at

the first international workshop on PET and lymphoma held in Deauville and is often referred to as the 'Deauville criteria' (Meignan, Gallamini, et al., 2009) (Table 2). The five point scale has good interobserver agreement (Sally F. Barrington et al., 2010; Biggi et al., 2013; Dupuis et al., 2012; Furth et al., 2011; Le Roux et al., 2011). The scale appears to improve the PPV (Dupuis et al., 2012; Le Roux et al., 2011; D.-H. Yang et al., 2011) if higher thresholds than the mediastinum are used to differentiate good from less good response whilst maintaining the high NPV compared with 2007 criteria, especially for interim scans. It is being used in response-adapted trials (RAPID, RATHL, HD0607,NCT0822120,IELSG37, identifiers in Table1) with the advantage that the threshold of FDG uptake chosen to define response can be higher for a trial involving escalation (to avoid risk of over-treatment) than a trial investigating de-escalation (to avoid under-treatment). Scores 1,2,3 were considered to represent a negative scan in the UK-led RATHL study with patients with scores 4,5 escalated to BEACOPP from ABVD. Scores 1, 2 were however used to define a negative scan in the UK RAPID study where patients with early stage non-bulky disease and a negative scan were randomised to radiotherapy or no further treatment after 3 cycles of ABVD.

The use of the five-point scale relies on consistency in scanning conditions for serial scans and attention to patient preparation, scan acquisition and the quality control of imaging equipment as well as reporting methods is crucial (Boellaard et al., 2010).

What confounding factors may affect the use of FDG PET in lymphoma management?

FDG is not specific for malignancy; uptake occurs in inflammatory cells and infection which also have increased glucose metabolism. Indeed it has been suggested that

one reason why FDG is a good biomarker in HL is its ability to image inflammatory cells in the tumour microenvironment (A Gallamini, 2010). Clinicians must be aware of potential confounding causes of increased FDG (S. F. Barrington & O'Doherty, 2003; Cook et al., 2004) including infection, inflammation, granulomatous disease (Figure 4), synchronous malignancy and physiological variants such as thymic hyperplasia. It is important to question findings that are at variance with the clinical course or where there is a 'mixed response' with apparent improvement in some areas of disease, but persistent or increased FDG uptake or new lesions elsewhere. These situations are best discussed in a multidisciplinary team.

What is the role in relapse and pre transplant assessment of PET?

PET can be used for restaging of patients at relapse as it is used in staging of de-novo lymphomas (Elstrom et al., 2008; Janikova et al., 2008; Schaefer et al., 2004). For patients undergoing autologous stem cell transplant (ASCT) for relapsed or refractory disease, a PET scan performed after salvage treatment has prognostic value. Patients with a positive scan are 3-7 times more likely to relapse or progress than patients with a negative scan (Terasawa et al., 2010). Series are mostly retrospective and have used different salvage regimens, but all appear to support a role for PET in pre-transplant assessment with ASCT with PFS rates of 23-41% reported for patients with residual uptake and 71-82% for patients with CMR (Devillier et al., 2012; Mocikova et al., 2011; Moskowitz et al., 2012; Smeltzer et al., 2011; Sucak et al., 2011). It remains controversial whether to offer transplantation to patients with less than CMR, with some series reporting successful outcomes in up to 40% of PET positive patients or to offer extended salvage therapy on the basis of a positive scan (Moskowitz et al., 2012). A PET response-adapted approach has recently been reported to select patients with HL for transplantation(Thomson et al.,

2013). Patients with CMR on PET, defined as scores 1-3 on Deauville criteria were offered ASCT following salvage, whilst patients who did not achieve CMR with at least stable disease and a suitable donor proceeded to allograft. 4y-OS for 61 patients in the study was 77% with 3-y PFS and OS of 86% and 93% respectively for patients undergoing ASCT and 68% and 88% undergoing allograft. PET is also a reliable early end-point which will prove valuable in testing novel agents such as SGN-35 (Hutchings, 2011). Post-transplant assessment with PET has been reported as being predictive of PFS/OS in a small study with 43 patients with HL (Sucak et al., 2011) but not in another study of 68 patients with HL and NHL (Palmer et al., 2011). Prior to reduced intensity conditioning allogeneic transplant, one study in a mixed population of 80 patients (Dodero et al., 2010) reported that PET status was predictive of PFS and OS, whilst another in mixed population of 80 patients did not (Lambert et al., 2010). The authors of the latter study reported that PET detected relapse post-allogeneic transplant earlier than CT and that PET might be a useful tool during surveillance to select PET positive patients for donor lymphocyte infusion. These patients experienced a low incidence of graft versus host disease.

Is there a role for PET in surveillance of patients ?

Relapses are more likely to be detected in symptomatic than asymptomatic patients (Goldschmidt et al., 2011) although surveillance scanning with PET has been reported to detect unsuspected relapses in up to 10% of patients with HL and aggressive NHL (Cheah et al., 2013; Pier Luigi Zinzani et al., 2007). Lead-time bias is a potential problem in studies reporting surveillance imaging as earlier detection of disease may give false impressions of longer survival. As yet, no data exist to demonstrate that earlier detection improves patient outcomes. The positive predictive value for surveillance scans is variable, ranging between 21% - 74% for

patients with HL and aggressive NHL in first remission (Avivi et al., 2013; Cheah et al., 2013; Tarec El-Galaly et al., 2011; Lee et al., 2010). False positive scans can lead to unnecessary biopsies and patient anxiety. The cost to detect a single event was estimated at US$100 000 in one study (Lee et al., 2010). CT was similarly associated with a low PPV of 29% but lower financial cost. The associated radiation burden must also be considered. Currently there is no clear evidence to support surveillance imaging with PET-CT. However, it may be justified in selected cases with high risk of relapse (Cheah et al., 2013; T El-Galaly et al., 2013).

What is the Radiation dose typically associated with PET-CT?

The effective dose for a half-body PET scan is 8mSv for 400MBq FDG, the UK diagnostic reference level ("Administration of Radioactive Substances Advisory Committee Notes for Guidance," 2006,revised 2011). With recent advances including 3D imaging, time of flight and better reconstruction algorithms, lower activities could be used or faster imaging times employed using the same activity. The effective dose could be reduced as low as 4-5 mSv with the most up-to-date cameras (Boellaard et al., 2010). If a low dose CT scan is used, the effective dose is 7-9mSv, with a combined effective dose of around 11-17mSv. This equates to 5-8 years of natural background radiation. The National Reference Dose Level for a full-dose contrast enhanced CT of the chest, abdomen and pelvis of 940 mGycm (Shrimpton et al., 2005) corresponds to an Effective Dose of approximately 16 mSv ("The 2007 Recommendations of the International Commission on Radiological Protection," 2007) which is comparable to a PET-CT examination.

What about the use of PET-CT for T-cell Lymphomas?

Most reports about PET-CT involve patients with B-cell malignancy but some reports in aggressive NHL have included patients with T-cell lymphomas. As a separate entity however, there are limited data reporting FDG-PET in patients with T-cell and NK cell lymphomas. Most are FDG avid, with higher uptake in more aggressive subtypes but lower uptake in cutaneous disease (Feeney et al., 2010; P. L. Zinzani, 2011). Patients with Mycosis Fungoides have higher FDG uptake in the presence of large cell transformation and it has been suggested that suspected transformation may be an indication for PET-CT, analogous to its use in Follicular Lymphoma (Feeney et al., 2010). Higher uptake is also seen in systemic manifestations of cutaneous lymphomas and a role in the detection of visceral involvement has been suggested as this alters management (Otero et al., 2009). Although PET also detects more lesions than CT in nodal and leukaemic variants of T-cell lymphomas, this rarely affects management (Casulo et al., 2013). Interim assessment with FDG was reported to be predictive of PFS, but not OS, in one study of 50 patients with peripheral T-cell lymphomas (Casulo et al., 2013), but not in another study involving 54 patients (Cahu et al., 2011); in the latter study the post-therapy scan was not predictive of outcome. It is important not to extrapolate data relating to B-cell lymphomas to patients with T-cell lymphomas. As yet, there is no clearly defined role for FDG-PET in this disease group with the possible exceptions of excluding visceral involvement with Mycosis Fungoides and suspected transformation. Because the numbers of patients are small, prospective multicentre trials are required. A UK study opened in 2012 investigating the response rate of CHOP versus gemcitabine, methylprednisolone and cisplatin and is prospectively

measuring the complete metabolic response rate in patients with T-cell lymphoma (Chemo-T, Table 1).

Conclusion

PET-CT has an important role in the modern management of lymphoma, including staging, response and remission assessment and the selection of patients with refractory/relapsed disease for transplantation with HL and NHL, summarised in Table 3.

The role of response-adapted treatment in HL and DLBCL according to interim PET is being explored in multicentre international trials. Preliminary reports from RAPID and H10 studies are emerging on the role of iPET in selecting patients who may not require radiotherapy in early stage classical HL but final reports of these studies are awaited. Data relating to the use of FDG in T-cell lymphomas is limited and further studies are required. In cutaneous T-cell lymphoma, PET does not have a routine role in staging or response assessment with the exception of the detection of visceral involvement in Mycosis Fungoides.

Figures

Figure 1 Coronal slices with low-dose CT (left), PET (middle) and fused (right) images are shown of a patient with HL. Note the PET and fused images are displayed to a maximum SUV of 10 (colour scale on far right of figure, CT Hounsfield units displayed in grey). The SUV fixed scale is used for reporting at our Centre.

Figure 2 Coronal slices (low-dose CT, PET and fused images) show focal uptake (arrowed) in the spleen which is not enlarged and has normal appearances on CT.

Figure 3 Sagittal slices (low-dose CT, PET and fused images) are shown of a patient with DLBCL and marrow involvement, pre (part A) and post treatment (part B). Note how some vertebrae eg T12 with increased uptake become photopaenic with ablation of marrow, whilst other vertebrae with normal uptake at baseline have increased uptake relative to baseline due to the effects of chemotherapy. The images demonstrate a 'mirror' effect.

Figure 4 Coronal slices (low-dose CT, PET and fused images) are shown of a patient with sarcoid-like reaction with a typical distribution of FDG uptake in nodes in the mediastinum and within the lung.

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Table 1 Registration details of selected Clinical Trials

Study group	Trial identifier	Patient group	Clinical trial registration details
GHSG	HD16	Early-stage HL	(http://www.clinicaltrials.gov/ NCT00736320)
GHSG	HD17	Early-stage HL	(http://www.clinicaltrials.gov/ NCT01356680)
UK-NCRI	RATHL	Advanced HL	http://www.clinicaltrials.gov/ct2/show/NCT00678327
GITIL	HD0801	Advanced HL	http://www.clinicaltrials.gov/ct2 /NCT00784537
GITIL	HD0607	Advanced HL	http://www.clinicaltrials.gov/ct2/show/NCT00795613
Rambam Health Care	RHC	Advanced HL	http://www.clinicaltrials.gov/ct2/show/NCT00392314
US-SWOG	SWOG0816	Advanced HL	http://www.clinicaltrials.gov/ct2/show/NCT00822120
LYSA	AHL11	Advanced HL	http://clinicaltrials.gov/ct2/show/NCT01358747
GHSG	HD18	Advanced HL	http://www.clinicaltrials.gov/ct2/show/NCT00515554
US-SWOG& CALG-B	NCT0822120	Advanced HL	http://clinicaltrials.gov/ct2/ NCT00822120
IELSG	IELSG37	Primary mediastinal B cell lymphoma	http://clinicaltrials.gov/ct2 /NCT01599559
UK-NCRI	Chemo-T	T cell lymphpma	http://www.clinicaltrials.gov/ct2/NCT01719835

Key to abbreviations

GHSG German Hodgkin Study Group

NCRI National Cancer Research Institute (UK)

GITIL Gruppo Italiano Terapie Innovative nei Linfomi

SWOG South Western Oncology Group

LYSA Lymphoma Study Association

CALG-B Cancer and Leukemia Group B

IELSG International Extranodal Lymphoma Study Group

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Table 2 – The Five point scale (5PS/Deauville criteria)
The 5PS scores the most intense residual uptake in a site of initial disease as: **1.** no uptake **2.** uptake ≤ mediastinum ** **3.** uptake > mediastinum but ≤ liver **4.** uptake moderately higher than liver **5.** uptake markedly higher than liver and/or new lesions X new areas of uptake unlikely to be related to lymphoma ***NOTE if MBP ≥ liver activity, the uptake within lesions should be compared with liver (uptake lesion < liver is score 2; lesion = liver is score 3)***

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Table 3 Indications and Benefits for using PET-CT in Lymphomas

Indication/s	Benefit/s
PRE-TREATMENT	
Staging of patients with FDG-avid Lymphomas	Increased staging accuracy especially for extranodal disease Improved treatment selection Improved accuracy of response assessment and improved reporter agreement for response scans
To direct biopsy in suspected transformation of FL	Improved disease characterisation and treatment selection
Assessment of bone marrow involvement in HL and DLBCL	Improved accuracy compared to biopsy Avoidance of morbidity associated with bone marrow biopsy
Radiotherapy planning for patients with HL and DLBCL	More refined definition of radiotherapy volume + less irradiation of normal tissue.

	Essential for techniques less than IFRT
DURING TREATMENT	
Mid-treatment imaging to monitor response in HL and DLBCL	More accurate monitoring of response than mid-treatment CT (and earlier assessment) No evidence to modify treatment as yet, but useful to detect poor or no response early
POST-TREATMENT	
End of treatment assessment in HL DLBCL and FL (unless patients have had mid-treatment imaging showing complete metabolic response) to confirm disease remission or to direct biopsy if residual disease is suspected	More accurate assessment of remission than CT especially in cases of CRu or PR Part of IWG criteria for response assessment Possible role to select patients for consolidation RT (e.g. advanced stage classical HL after BEACOPP)
RELAPSE	
Pre-transplant assessment in patients undergoing ASCT with HL or DLBCL	More accurate and prognostic than CT

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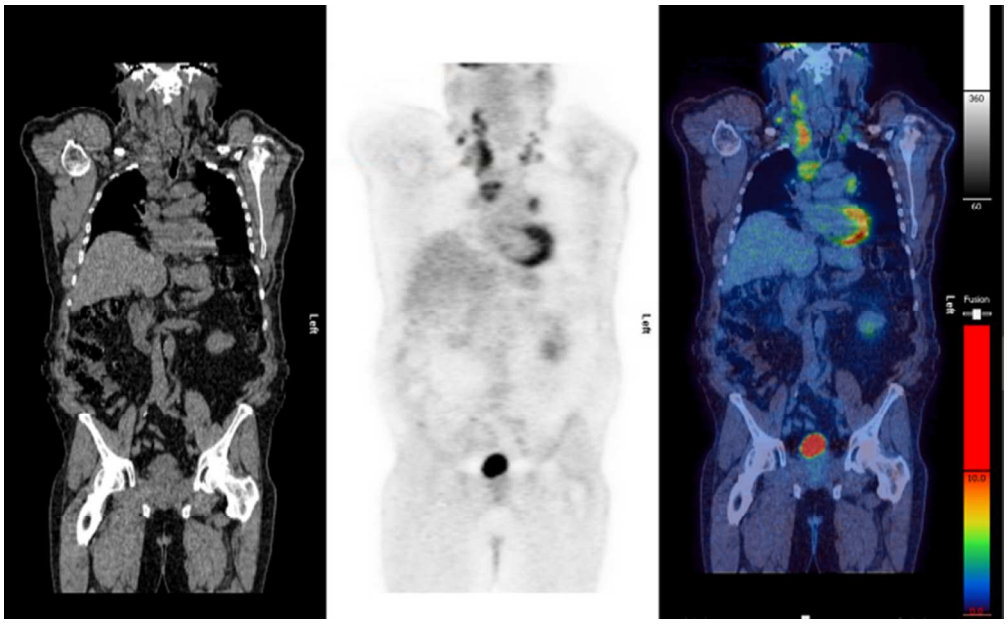

Coronal slices with low-dose CT (left), PET (middle) and fused (right) images are shown of a patient with HL. Note the PET and fused images are displayed to a maximum SUV of 10 (SUV colour scale on far right of figure, CT Hounsfield units displayed in grey). The SUV fixed scale is used for reporting at our Centre.
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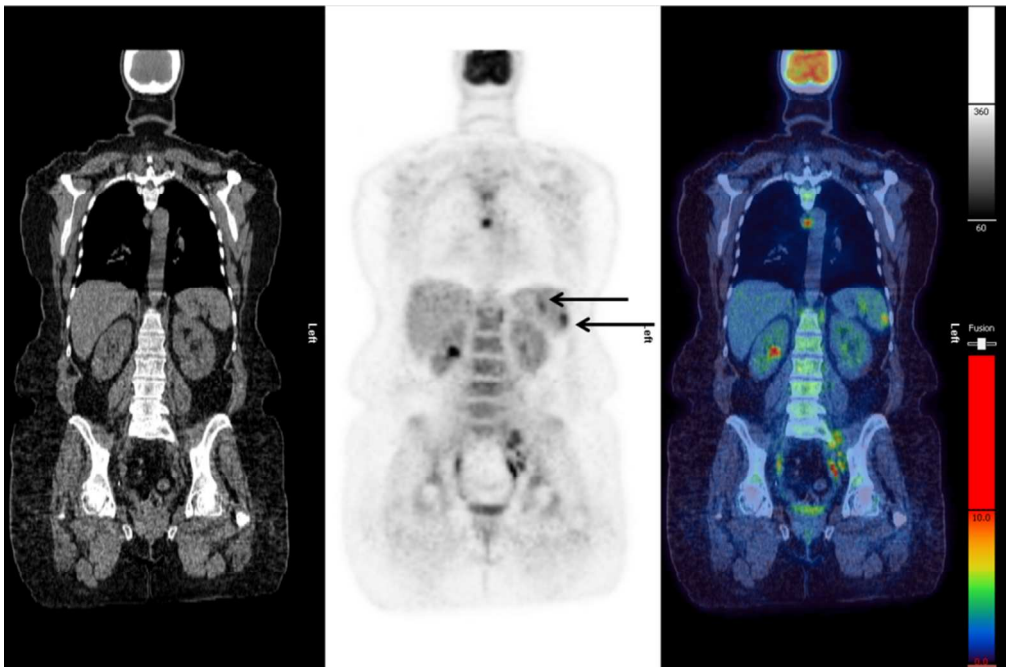

Coronal slices (low-dose CT, PET and fused images) show focal uptake (arrowed) in the spleen which is not enlarged and has normal appearances on CT.
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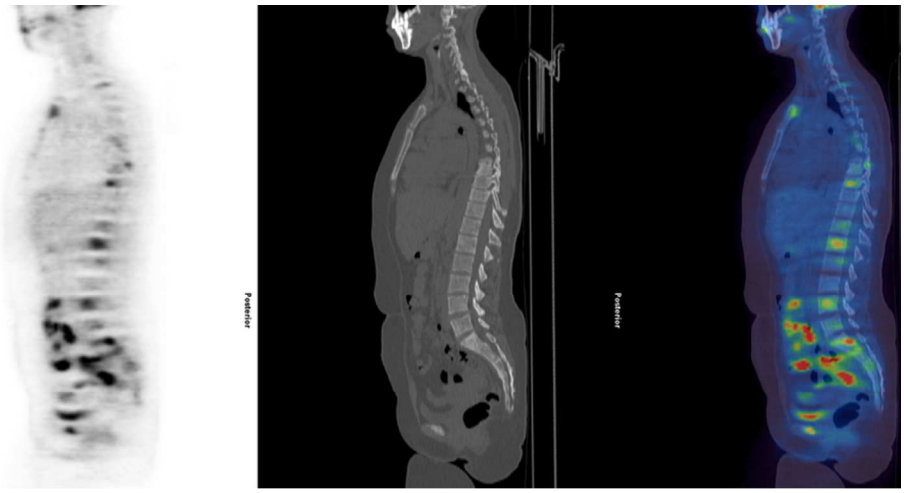

Sagittal slices (low-dose CT, PET and fused images) are shown of a patient with DLBCL and marrow involvement, pre (part A) and post treatment (part B). Note how some vertebrae eg T12 with increased uptake become photopaenic with ablation of marrow, whilst other vertebrae with normal uptake at baseline have increased uptake relative to baseline due to the effects of chemotherapy. The images demonstrate a 'mirror' effect.
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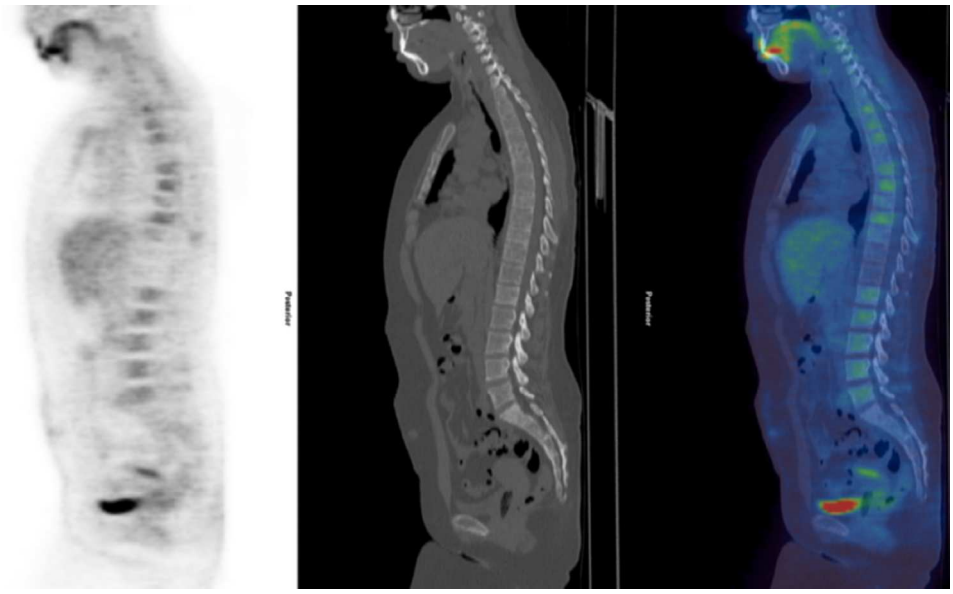

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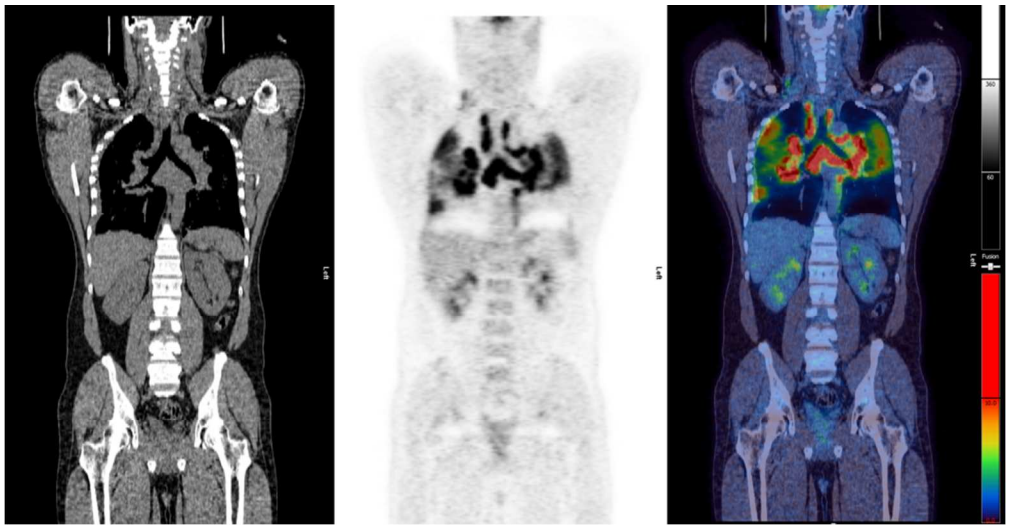

Coronal slices (low-dose CT, PET and fused images) are shown of a patient with sarcoid-like reaction with a typical distribution of FDG uptake in nodes in the mediastinum and within the lung.
84x43mm (300 x 300 DPI)